Statistical Parametric Mapping Analysis of Positron Emission Tomography Images for the Detection of Seizure Foci: Results in Temporal Lobe Epilepsy

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ABSTRACT

STATISTICAL PARAMETRIC MAPPING ANALYSIS OF POSITRON EMISSION TOMOGRAPHY IMAGES FOR THE DETECTION OF SEIZURE FOCI: RESULTS IN TEMPORAL LOBE EPILEPSY. Jeffrey R. Tseng, Rajesh Krishnamurthy, Douglas Bremner, Susan S. Spencer, Dennis D. Spencer, Holley M. Dey. Section of Nuclear Medicine, Department of Diagnostic Radiology, Yale University, School of Medicine, New Haven, CT.

The purpose of this study was to determine the efficacy of statistical parametric mapping (SPM) of [18F]-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) images of the brain for the localization of seizure foci in patients with temporal lobe epilepsy (TLE).

Preoperative PET brain scans from 36 patients with TLE and from 8 healthy control subjects were retrospectively analyzed with SPM95 software written for Matlab version 4.2. Scans were transformed to Talairach space, globally normalized, and smoothed. Differences between each patient's scan and the control group were then computed with the t statistic on a voxel by voxel basis. SPM maps were thresholded at $p < 0.001$ and reviewed for areas of significant hypometabolism relative to the control group. All 44 clinical 18FDG brain scans were also visually interpreted and regions of metabolic asymmetry noted. Localization of the seizure focus by both SPM and visual analyses were compared with each patient's temporal lobe resection site and with that patient's post-surgical outcome. A good post-surgical outcome was defined as ≥ 90% reduction in seizure frequency six months after operation.

SPM analysis predicted the surgical excision site in 32/36 patients (89%); visual analysis also correctly lateralized the temporal lobe resection site for 32/36 patients (89%). The SPM and visual analyses were concordant in 30/36 (83%) cases; both provided a false negative result in one cases. Of the 36 TLE patients, 31 had a successful surgical outcome with ≥ 90% reduction in seizure frequency six months after surgery. SPM analysis identified the temporal lobe seizure focus in 28/31 of these patients (90%). Visual analysis

identified 29/31 (94%). Of the 5 patients with poor surgical outcome, SPM analysis showed significant contralateral frontotemporal hypometabolism in 3 cases, and contralateral perihippocampal localization in 2 cases.

We conclude that SPM analysis of 18FDG PET images is useful for the localization of temporal lobe seizure foci in clinical and research settings. SPM provides a more objective and consistent means of image analysis for the evaluation of patients with epilepsy, particularly for inexperienced observers. Our data suggests that SPM analysis may also prove useful for the prediction of clinical outcome after temporal lobe resection.

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I would also like to thank Dayton Rich for his technical advice, Dr. Douglas Bremner for his assistance with SPM software, Dr. Susan Spencer for providing clinical data and input, Judith Hess for providing access to clinical patient data, and Dr. Dennis Spencer for providing surgical data.

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INTRODUCTION

Background - Clinical Epilepsy

Epilepsy is a term used to describe a diverse collection of disorders that affects more than one percent of the population of the United States (1). These disorders are characterized by episodic abnormal, paroxysmal electrical discharges within the brain that are manifested as recurrent, spontaneous seizures (2). Seizures that begin within a localized region of the brain cortex are termed "partial". Generalized seizures diffusely involve both cerebral hemispheres at the onset.

While a simple partial seizure does not impair the level of consciousness, a complex partial seizure is associated with loss of contact (1). This impairment of consciousness can be disabling for patients who suffer from recurrent and unpredictable complex partial seizures, and can lead to poor school/work performance, and eventually an inability to function independently (3). For some patients, medical treatment may be sufficient to control seizure activity. However, many patients have intractable complex partial epilepsy that cannot be controlled with reasonable doses of medication at tolerable levels of side effects. These patients may benefit from surgical excision of the epileptogenic focus in the brain, if this focus can be well localized.

Medically refractory patients comprise approximately 10-20% of the more than two million people in this country with epilepsy (4). Of these, up to 50% have complex partial seizures that are potentially localizable, and therefore amenable to surgical therapy. The majority of complex partial seizures appear to arise from the temporal lobe (1). Following temporal lobe surgery approximately 50-70% of patients with complex partial seizures become seizure free, 10-30% are significantly improved, and the remaining 15-30% show little or no improvement (5,6).

Localization of Epileptic Foci

Selection of a patient with complex partial epilepsy for surgical therapy requires that the abnormal electrical discharges within the brain be clearly and consistently localized to a specific brain region. The presurgical evaluation of patients who are considered for epilepsy surgery is completed in stages. During the first stage, non-invasive testing is performed to screen patients and to plan additional testing for those patients who may be surgical candidates. During the second and third stages, progressively more invasive testing is performed for those patients whose Stage 1 localization is ambiguous. This invasive testing includes intracranial electroencephalographic (EEG) monitoring (7).

The Stage 1 evaluation includes a thorough medical history and physical examination, neuropsychological testing, ictal and interictal scalp EEG recordings, and a series of imaging studies. The medical history may describe clinical features of the patient's epilepsy that are consistent with lateralization or localization of the seizure focus. The neuropsychological tests are used to identify areas of intact and/or impaired cognitive function that may be associated with an identified epilepsy syndrome (7).

Scalp ictal and interictal EEG recordings have classically been the mainstay of seizure diagnosis and localization. The first epilepsy surgeries relied primarily on interictal EEG identification of the seizure site. While the interictal scalp EEG remains an important part of the diagnostic work-up of patients with epilepsy, the technique can reveal ambiguous patterns and incorrect localization. Seizure foci may also remain undetected (8,9). Video EEG recordings permit correlation of the patient's ictal EEG pattern with clinical behavior. This data can enhance the probability of accurately localizing the seizure focus. However, the ictal EEG may falsely lateralize the seizure focus due to muscle/movement artifact, rapid spread of abnormal electrical activity to bilateral or remote

brain areas, or seizure onset in a deep brain region (7). In these cases, non-invasive imaging studies may provide critical localizing information.

Radiographic and nuclear medicine studies can detect structural and functional abnormalities in the brain that are correlated with epileptic seizure foci (2). Structural imaging includes computed tomography (CT) and magnetic resonance imaging (MRI); functional imaging includes single photon emission computed tomography (SPECT) and positron emission tomography (PET). MRI and CT can identify small structural lesions such as hamartomas, gliomas, and vascular malformations that may be the cause of seizure activity. MRI may also define structural abnormalities within the temporal lobe and/or hippocampus in patients with probable temporal lobe epilepsy. SPECT can detect regional hypoperfusion in patients with lateralized epilepsy, with a sensitivity of 66% for temporal and 60% for extratemporal lobe epilepsy. PET is used to identify focal hypometabolism in the region of the seizure focus; a sensitivity of 84% has been reported for temporal lobe epilepsy, 33% for extratemporal lobe epilepsy. Where available, interictal PET is preferred for functional imaging of the patient with suspected temporal lobe epilepsy.

Stage 1 evaluation of the patient with potentially localizable epilepsy now includes a conglomeration of clinical, EEG, and imaging tests. When the summed data, including surface EEG and imaging tests, provide a concordant seizure site localization, some epilepsy surgery centers now proceed directly to surgical resection, circumventing the need for more invasive intracranial EEG recording with its attendant surgical risks of cerebral infection and hemorrhage (10-12).

Positron Emission Tomography

PET imaging uses very small amounts of positron emitting radiopharmaceuticals to identify and measure tissue function. Short-lived radioactive isotopes of elements such as

carbon, oxygen, nitrogen, and fluorine are chemically "tagged" to compounds of physiologic importance; these radiopharmaceuticals are then internally administered to the patient. Organ specific uptake of the radiopharmaceutical is based upon the chemical structure of the injected compound. For example, [11C]acetate, a marker of myocardial oxidative metabolism, is targeted for and avidly extracted by heart muscle. A specialized PET camera is then used to detect and record the annihilation photons that result when the administered positrons interact with tissue electrons in the organ of interest (13,14). Images of the distribution of the positron emitting radiopharmaceutical within tissue are generated through a complex mathematical process known as filtered back projection. The resulting image is a cross-section of the tissue or organ, with the intensity of each pixel element proportional to the concentration of the radiopharmaceutical at that position in the body.

Patients with epilepsy have been successfully imaged with the PET radiopharmaceutical [18F]fluoro-2-deoxyglucose (FDG), an analog of glucose (15). FDG, like glucose, is actively extracted into brain tissue, and is phosphorylated by hexokinase in the first step of the glycolytic pathway. Unlike glucose, FDG is not further metabolized and is essentially trapped in tissue. Images of FDG distribution within the brain therefore reflect regional cerebral glucose utilization, with the highest concentrations of radiopharmaceutical found in areas of greatest metabolic activity.

PET images reveal reduced interictal cerebral glucose metabolism in patients with epilepsy (15-18). This evidence is particularly strong for patients with complex partial seizures of temporal lobe origin. A recent retrospective review of the literature showed that asymmetrically decreased metabolic activity within the temporal lobe accurately localizes the seizure focus in patients with complex partial epilepsy. The sensitivity of FDG PET for temporal lobe epilepsy as compared to an EEG gold standard was 84%, with a specificity of 86% (1).

Compared to a tissue pathology gold standard, the sensitivity of PET for temporal

lobe epilepsy was 81%, with a specificity of only 22%. This lower specificity may represent extension of PET hypometabolism beyond the pathology defined seizure site, consistent with a larger area of functional disturbance within the brain than would be expected on the basis of structural changes alone. Analysis of the distribution of radiolabeled FDG within the temporal lobe has had varying results; recently, Hajek *et al* related tissue pathology to FDG distribution within the temporal lobe (1). Patients with medial temporal lobe epilepsy showed diffuse temporal lobe hypometabolism; patients with temporal neocortical epilepsy had more limited hypometabolism within the lateral temporal cortex.

Several studies have related PET findings to surgical outcome in epilepsy. PET hypometabolism predicts a favorable clinical outcome for 71-96% of patients (20-23). It should be noted, however, that published studies lack consistency in the method of PET data analysis and in the definition of a "good" surgical outcome after epilepsy surgery. Table 1 summarizes these studies.

PET Image Analysis

PET image analysis can be performed by qualitative or quantitative means. Qualitative analysis consists of the identification of regions of hypometabolism through visual interpretation. In patients with suspected temporal lobe epilepsy, FDG PET images of the temporal lobes are carefully examined for global and/or regional asymmetries in radiopharmaceutical uptake. Left is compared to right in order to detect areas of abnormality. A rough measure of the severity of hypometabolism can be made by judging the degree of asymmetry between the abnormal temporal lobe and the presumably normal contralateral side.

Visual qualitative analysis is necessarily subjective and requires the observer to

Study	No. of Patients	No. of Good Outcome	No. of Poor Outcome	Definition of Good Surgical Outcome
Heinz *et al* (20)	24	17 (71%)	7 (29%)	> 90% reduction, < 10 seizures/year
Manno *et al* (21)	35	29 (83%)	6 (17%)	seizure free
Radtke *et al* (22)	25	24 (96%)	1 (4%)	> 75% reduction of seizures
Theodore *et al* (23)	42	35 (83%)	7(27%)	seizure free

Table 1. Summary of studies comparing PET imaging with surgical outcome for patients with temporal lobe hypometabolism and subsequent temporal lobectomy.

pinpoint differences in image intensity in order to identify a region of abnormality. The observer is also asked to relate areas of abnormality to regional brain anatomy. These tasks may prove difficult for an inexperienced reader (24). Qualitative interpretation of FDG PET can also be complicated by a bilateral temporal or diffuse reduction in metabolism that precludes identification of a metabolic asymmetry. For example, global hypometabolism that results from use of antiepileptic drugs (AED) may mask localized epileptic foci (25).

PET images of regional cerebral glucose metabolism can also be quantified. Quantification can lend objectivity to image analysis that is not possible through visual interpretation. Quantification requires a computer based region of interest analysis to determine the concentration of radioactivity within user defined regions of interest in the temporal lobe and whole brain. Radioactivity concentration can be described as: 1) an absolute measurement, with the local cerebral glucose metabolic rate given in units of mg/100 gm/min ; 2) a ratio of activity in the region of interest to activity in a normal area of metabolism. The "normal" area might be the homologous contralateral brain cortex, or an area such as the cerebellum that is presumably unaffected by the temporal lobe epilepsy process.

Absolute quantification of the cerebral glucose metabolic rate can be performed using a model developed by Sokoloff *et al* and is based upon knowledge of the arterial input function into the brain and plasma glucose concentration (26). Calculation of an absolute metabolic rate therefore requires serial blood samples from the patient to determine the amount and time course of delivery of injected radiopharmaceutical to the brain, as well as the plasma glucose concentration. Problems with absolute value analysis are the necessary complexity of the analysis, the requirement for frequent invasive blood draws, and possible confounding of the results by AED use (27,28). Quantitative analysis is also plagued by compromises between sensitivity and specificity when determining appropriate threshold values for normality (21,29). In addition, semi-quantitative ratio analysis is

problematic since bilateral and/or global hypometabolism can deter attempts to identify a localized focus of abnormality.

The purpose of this research project was to evaluate the utility of a new tool, statistical parametric mapping analysis (SPM) of FDG PET, for the detection of seizure foci in patients with complex partial epilepsy. SPM refers to the construction of statistical maps of change significance, in which the patient's images of cerebral glucose metabolism are compared on a voxel by voxel basis to images from a group of healthy controls such that areas of significant difference are highlighted. SPM has several theoretical advantages over current methods for FDG PET brain image analysis. These include substantial elimination of subjectivity in image analysis, more precise anatomic localization of functional abnormalities, and avoidance of blood sampling. Additionally, bilateral and global changes in metabolism are not masked as each patient can be compared to a normal healthy control population.

Statistical Parametric Mapping

Statistical parametric mapping (SPM) has been used to evaluate PET images of regional cerebral blood flow and metabolism and to identify significant changes from the patient's own baseline or from healthy control subjects (30-32). Applications for SPM have been reported in PET studies of memory, sensory and motor activation, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (33-37). Based on these reports, we believed that SPM analysis would prove useful for the detection of abnormal temporal lobe metabolism.

STATEMENT OF PURPOSE

The primary objective of this study was to compare the utility of statistical parametric mapping (SPM) analysis to visual interpretation of FDG PET brain images for the detection of seizure foci in patients with complex partial epilepsy. A secondary objective was to determine the relationship between the SPM defined seizure focus and clinical seizure outcome following epilepsy surgery.

We hypothesized that SPM analysis would prove more sensitive than visual analysis for the detection of seizure foci and for the prediction of post-operative seizure outcome in patients with complex partial epilepsy, based on the greater objectivity and greater potential sensitivity of the statistical method.

METHODS

Patient Selection

From January 1992 to June 1996, 156 patients with complex partial seizures of presumed temporal lobe origin were referred to the Yale-VA PET Center for imaging of regional cerebral glucose metabolism. Of this number, 80 patients subsequently underwent temporal lobectomy and had at least six months of clinical follow-up data available at the time of this study. From this group of subjects, 28 patients with known neoplastic or vascular lesions within the temporal lobe as identified from pathology, biopsy, or MRI reports were excluded. Image data could be retrieved for 36 of the remaining 52 patients. These 36 PET image data sets were retrospectively reanalyzed, and the results compared with each patient's surgical resection site and post-surgical outcome.

There were 18 men and 18 women in the group of epilepsy patients. Mean patient age at the time of PET imaging was 35.1 yrs. (range 9.2 - 55.3 yrs.). The mean duration of illness was 28.7 yrs. (range 4.2 - 51.0 yrs.). Average age of seizure onset was 6.4 yrs. (range 0 - 36 yrs.).

Image data from 8 healthy control subjects were also retrospectively reviewed and reanalyzed. The healthy control subjects were eight men with a mean age of 44 (range 25 - 60). Healthy subjects had no history of significant medical disease, and specifically no neurologic or psychiatric complaints. Each control subject provided a complete medical history, underwent a physical examination, and had normal serum chemistry and hematology tests prior to inclusion in the normal database. These patient studies were approved by the V.A. Institutional Review Board protocol under the direction of Dr. Douglas Bremner.

Presurgical evaluation for all epilepsy patients included ictal and interictal surface

EEG and PET scan. In addition, intracranial EEG, MRI, ictal and interictal SPECT, neuropsychiatric testing, and cerebral angiography may have been performed during the course of the staged pre-surgical evaluation.

All 36 epilepsy patients underwent temporal lobectomy. The standard surgery was an anteromedial temporal lobectomy with hippocampectomy. The extent of tissue resection differed between patients, and was based on the results of pre-surgical testing. There were a total of 24 left sided resections and 12 right sided.

PET Imaging

PET studies were performed on a Posicam 6.5 whole body camera (Positron Corporation, Houston, Texas). Patients were positioned in the camera gantry with the orbital meatal line oriented to the x-y plane. An intravenous injection of 10 mCi of 18-FDG was then administered. During radiopharmaceutical injection the patient's eyes remained open and the camera room was dimly lit. Extraneous noise was minimized, and soft background music was played during and after dose administration. Forty-five minutes were allowed for clearance of FDG from the blood pool and uptake into brain. Image data were subsequently acquired until approximately 60 million positron annihilation events were recorded (approximately 20 min.). Two overlapping brain scans were obtained for each patient in order to maximize the likelihood of obtaining high quality images of the temporal lobes.

The axial field of view of the camera was 11.5 cm. Twenty-one image slices were acquired, separated by 5.125 mm with an axial resolution of 11 mm. In plane resolution was 5.7 mm (full width at half maximum). A theoretical attenuation correction was applied to the acquired image data; a uniform attenuation coefficient of 0.096 cm^{-1} was applied. Transverse image reconstruction was performed using filtered backprojection with a

Butterworth ß filter using a cutoff of 0.04, cutoff fraction of 0.306, and filter order of 10.0. Images were reconstructed in a 256 x 256 matrix with a pixel size of 1.7 mm. Reoriented tomograms were displayed in the axial, coronal, and sagittal planes. A graded color display was normalized to the area of maximum activity. Each change (gradation) in color represented a 5% difference in normalized intensity.

PET Visual Analysis

PET brain images were visually interpreted by an experienced nuclear medicine physician (H.M.D.) who was blinded to the patients' clinical information, except the knowledge that patients had a surgical epilepsy procedure. Visual analysis involved careful review of each patient's PET scan with comparison of relative FDG uptake within homologous brain regions utilizing the graded color display. Areas of relative hypometabolism were recorded on data sheets (see Appendix). For each abnormal region the affected lobe/structure (temporal, frontal, parietal, occipital, cerebellum, thalamus, basal ganglia) was noted, and the distribution of hypometabolism within that region (medial /lateral, anterior/posterior, and superior/inferior) was defined. An asymmetry index was generated for each abnormal brain region by comparing FDG uptake within the hypometabolic lobe to uptake within the contralateral homologous brain tissue. The asymmetry index was based upon the graded color image display scale. Differences in uptake between the temporal lobes, for example, was recorded as: None (< 5% asymmetry in uptake on the graded color scale), Minimal (5-10% asymmetry), Mild (10-15% asymmetry), Moderate (15-20% asymmetry), or Severe (>20% asymmetry). When both homologous brain regions appeared hypometabolic, an additional measure of uptake, termed the "absolute index", was generated by comparing activity within the regions of abnormality to uptake within a presumably normal area of brain metabolism (typically the

cerebellum). For each patient's PET scan an overall reading was generated, with the area of most significant hypometabolism defined as the likely seizure site.

PET SPM Analysis

Image data from all 36 patients with temporal lobe epilepsy and from the 8 healthy control subjects were transferred to a SUN SPARC station 10 for SPM analysis. The image data were analyzed using SPM95 software written for Matlab version 4.2. Preprocessing of the data prior to statistical analysis was required. All scans were transformed into Talairach space based on an automated computer definition of the anterior-posterior commissural line. This procedure ensured that functional brain abnormalities could consistently be mapped to brain anatomy using the Talairach stereotaxic brain atlas. Data sets were then globally normalized to correct for individual differences in the injected dose of radioactivity, and smoothed. A statistical analysis of the data sets was performed. Each patient's PET scan was compared against data sets from the 8 healthy control subjects on a voxel by voxel basis with computation of the t statistic. A statistical map representing change significance between the patient's PET scan and the normal database was generated and thresholded at $p < 0.001$. Voxels with z scores > 3.0 ($p < 0.001$) were highlighted on coronal, axial, and sagittal image displays. An experienced nuclear medicine physician (H.M.D.) then visually analyzed the SPM maps to describe areas of regional hypometabolism. The likely seizure site was defined as that localized brain region demonstrating the most significant hypometabolism on SPM map. Where present, extension of hypometabolism to include remote areas of brain cortex was described in the SPM interpretation.

Statistical Analysis for Localization and Surgical Outcome

Both the visual and SPM analyses of the PET data were retrospectively compared to each patient's chosen surgical site. The sensitivity of both visual and SPM analyses for localization of the seizure site as defined by the surgery gold standard was calculated. The PET analyses were considered to have provided a true positive localization if the major identified focus of hypometabolism matched the surgical site, regardless of the presence of additional, less significant areas of hypometabolism. When homologous brain regions were bilaterally abnormal, the more hypometabolic side was labeled as the likely seizure focus.

Both visual and SPM PET data analyses were also compared with the patients' post-surgical outcome data. For this purpose, a good surgical outcome was defined as a greater than 90% reduction in seizure frequency 6 months after operation. Thirty-two of the 36 patients were evaluated at $\geq$ 1 year after surgery. A poor surgical outcome was considered less than a 90% reduction in seizure activity. For both visual PET interpretation and SPM analysis positive predictive values were calculated. The sensitivities and positive predictive values of the PET analyses for surgical outcome were compared using the McNemar test.

Pathology Analysis

For 33/36 epilepsy patients the results of histopathologic examination of the resected brain tissue were available. Abnormal findings within the resected temporal lobe were recorded and variably classified as hippocampal sclerosis, non-hippocampal gliosis, congenital abnormality (e.g. heterotopia), or other. Histopathology findings were then compared with the regional cerebral distribution of hypometabolism defined by visual and statistical analyses of the PET image data.

Contributors

The majority of clinical and PET data collection, data entry, data processing, and analysis was performed by the author. Rajesh Krishnamurthy, M.D. assisted with collection of clinical data, as well as acquisition and processing of image data. Dayton Rich, C.N.M.T. assisted with retrieval of PET image data for analysis. Judith Hess assisted with collection of clinical data. Holley Dey, M.D. performed visual interpretation of the PET images. Dr. Dey also assisted in the processing of SPM data and interpreted the SPM images. Doug Bremner, M.D. assisted with the acquisition and processing of image data from eight healthy control subjects for the SPM analysis.

RESULTS

PET Imaging Results

Results of the visual analysis of the FDG PET scans are provided in Table 2. Temporal lobe hypometabolism was identified in 33 of 36 patients. One patient had regional hypometabolism limited to the frontal lobe. Two patients had PET scans that were interpreted as showing no focal abnormality. Relative temporal hypometabolism was visually graded as follows: a severe asymmetry was found in 12 cases, moderate asymmetry in 8, mild asymmetry in 11, and minimal in 2 cases. Extratemporal ipsilateral extension of hypometabolism was identified in 21 patients for a total of 29 extratemporal sites. Extratemporal hypometabolism was described as follows: a frontal lobe abnormality was found in 13 patients, parietal lobe in 8, occipital lobe in 5, thalamic hypometabolism was noted in 1, basal ganglia abnormality in 2 cases. Bilateral temporal lobe hypometabolism was present in 5 patients.

Table 2 describes the results of the SPM analysis of the FDG PET data. Temporal lobe hypometabolism was present in 35/36 patients. Of these, 21 regions of hypometabolism were classified as frontotemporal and 3 as temporooccipital. One patient had a discrete occipital lobe abnormality. There were no normal scans. Bilateral extension of hypometabolism was found in 29 patients. Visual analysis of the SPM maps graded the extratemporal extension of hypometabolism as follows: severe extension in 8 cases, moderate in 6, mild in 7, and minimal in 7 cases. The location of the extensions were as follows: frontotemporal in 20 cases, frontal in 4, temporal in 3, and temporooccipital in 2 cases.

		Visual Analysis		SPM Analysis		
Surgical Outcome	Surgical Site	Side	Location	Major Region	Bilateral Extension	Pt. No.
Good	Left	-	**normal**	L frontotemp	severe R frontotemp/perihipp	1
Good	Left	B (L>R)	temp	L temp	mild R front	2
Good	Left	B (L>R)	temp + front	L frontotemp	mild R frontotemp	3
Good	Left	B (L>R)	temp + front	L frontotemp	severe R frontotemp	4
Good	Left	Left	temp	L frontotemp	min R front	5
Good	Left	Left	temp	L frontotemp	min R frontotemp	6
Good	Left	Left	temp	L frontotemp	mod R frontotemp	7
Good	Left	Left	temp	L frontotemp	mod R frontotemp/perihipp	8
Good	Left	Left	temp	L frontotemp	none	9
Good	Left	Left	temp	L frontotemp	severe R frontotemp	10
Good	Left	Left	temp	L temp	none	11
Good	Left	Left	temp + front	L frontotemp	mild R temp	12
Good	Left	Left	temp + front	L frontotemp	mod R frontotemp	13
Good	Left	Left	temp + front	L frontotemp	none	14
Good	Left	Left	temp + front	L frontotemp	severe R frontotemp/perihipp	15
Good	Left	Left	temp + front + parietal	L temp	min R front	16
Good	Left	Left	temp + occip + BG	L temporooccip	min R frontotemp	17
Good	Left	Left	temp + parietal	L frontotemp	min R front	18
Good	Left	Left	temp + parietal	L temp	none	19
Good	Left	Left	temp + parietal + occip	L frontotemp	mod R temp	20
Good	Left	Left	temp + parietal + occip + front	L temp	min R frontotemp	21
Good	Right	**B (L>R)**	**temp + front + thalamus**	**L temp**	mild R frontotemp	22
Good	Right	Right	temp	R frontotemp	severe L frontotemp	23
Good	Right	Right	temp	R temp	none	24
Good	Right	Right	temp	R temp	none	25
Good	Right	Right	temp + front	**L frontotemp**	mild R frontotemp	26
Good	Right	Right	temp + front	**L occip**	none	27
Good	Right	Right	temp + front + occip	R frontotemp	mod L frontotemp	28
Good	Right	Right	temp + front + parietal	R temporooccip	mod L tempoccip	29
Good	Right	Right	temp + parietal	**L temp**	severe R frontotemp	30
Good	Right	Right	temp + parietal	R temp	min L frontotemp	31
Poor	Left	B (L>R)	temp	L temp	mild R temp/perihipp	32
Poor	Left	**Left**	**frontal + BG**	L frontotemp	mild R frontotemp/perihipp	33
Poor	Left	Left	temp	L frontotemp	severe R frontotemp	34
Poor	Right	-	**normal**	R temporooccip	severe L tempoccip	35
Poor	Right	Right	temp + occip	R frontotemp	severe L frontotemp	36

Table 2. Results of surgical site, surgical outcome, visual PET analysis, and SPM PET analysis. For surgical outcome, "good" represents ≥ 90% seizure reduction at a minimum of 6 months follow-up; "poor" represents < 90% seizure reduction. Surgical site lists the side of the temporal lobectomy. Visual analysis lists side and location of hypometabolism. SPM Analysis lists side and location of the major region of hypometabolism along with significant bilateral extensions and degree. PET analyses which do not agree with surgical site are **highlighted**. Abbreviations: B = bilateral; L = left; R = right; temp = temporal lobe; parietal = parietal lobe; occip = occipital lobe; front = frontal lobe; min = minimal; mod = moderate; perihipp = perihippocampal region.

Localization of Epileptic Foci Analysis

Visual analysis was concordant with the surgical site in 32/36 (89%) cases. Two scans were normal (Patients 1 and 35). One patient was incorrectly lateralized (Patient 22). One patient was localized to the wrong lobe of the brain (Patient 33).

SPM analysis was also concordant with the surgical site in 32/36 (89%) cases. Four patients were incorrectly lateralized (Patients 22, 26, 27, 33). Patient 33 was incorrectly lateralized by both visual and SPM analyses. The SPM and visual analyses were concordant in 30/36 (83%). There was no difference between the sensitivities of visual vs. SPM analyses for detection of the temporal lobe resection site.

Surgical Outcome Analysis

Favorable clinical outcomes were reported for 31 of 36 (86%) patients. Visual analysis identified 29/31 (94%), while SPM analysis identified 28/31 (90%) cases. Figures 1 and 2 show clinical PET and SPM image data from Patient 16 with a good surgical outcome. There was no statistically significant difference between the positive predictive values of PET visual and SPM analyses for favorable post-surgical outcome.

Five patients had poor surgical outcomes, with frequent recurrent seizures. One of these patients had bilateral temporal lobe hypometabolism by visual analysis. SPM revealed severe contralateral temporal hypometabolism in 3 cases (e.g. Patient 34 in Figure 3) and contralateral perihippocampal hypometabolism in 2 cases (e.g. Patient 32 in Figure 4).

Of the five patients considered to have bilateral temporal hypometabolism on visual analysis, one had a poor clinical outcome. Of the 29 patients with bilateral temporal abnormalities on SPM analysis, 5 had a poor outcome. Of patients with severe bilateral extension of hypometabolism on SPM, 3/9 showed no improvement after epilepsy surgery.

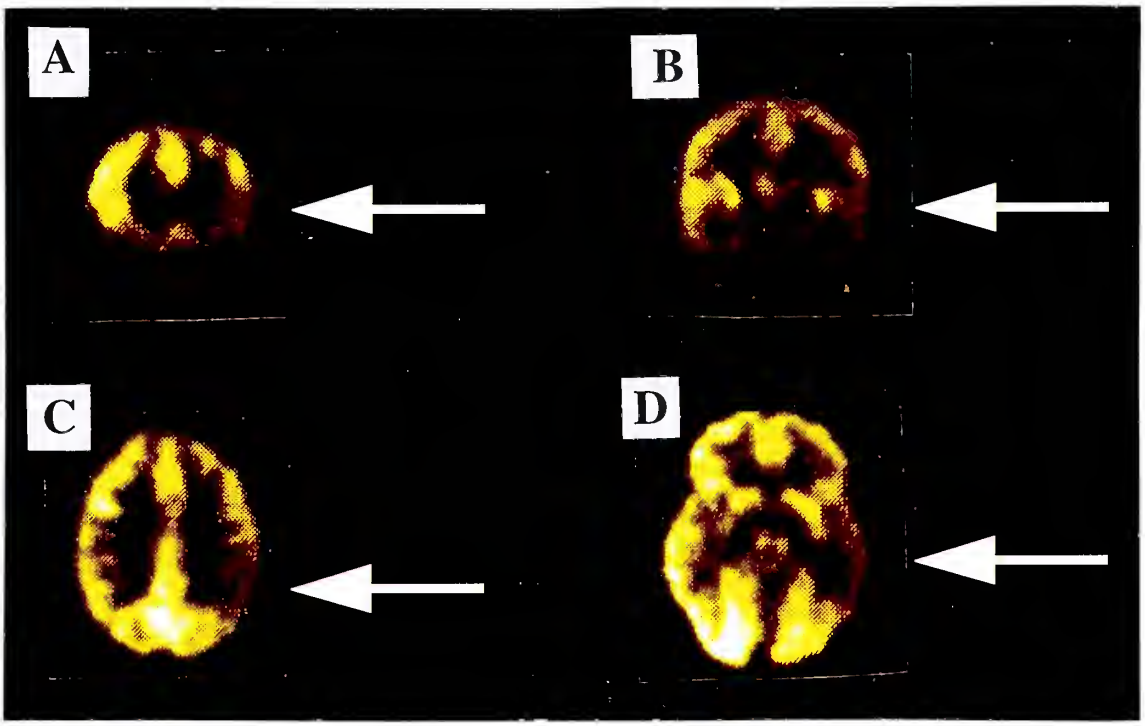

Figure 1. PET image for visual analysis from Patient 16 with a good surgical outcome. Two coronal slices (A, B) and two transaxial slices (C, D) are shown. Left temporal lobe hypometabolism is evident in B and D. There is also frontal (A) and parietal (C) hypometabolism.

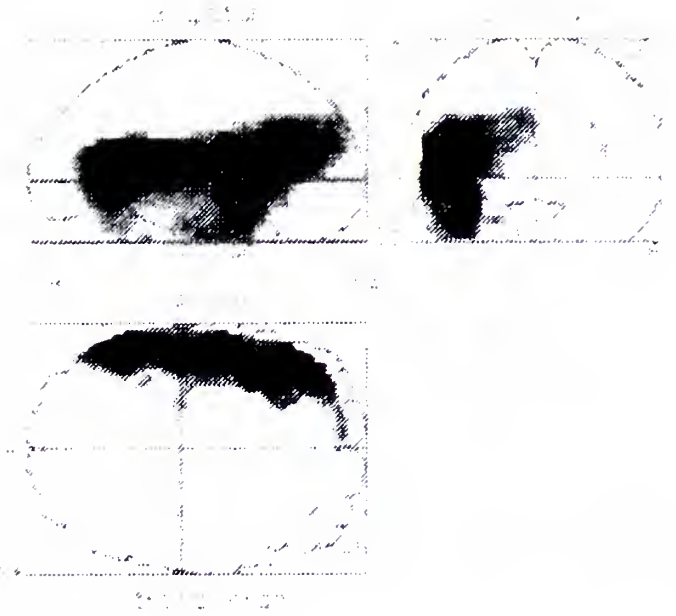

Figure 2. PET image for SPM analysis from Patient 16 with a good surgical outcome. The surgery was located on the left side, and the pathology report revealed hippocampal sclerosis. Sagittal, coronal, and transaxial views are shown. On the coronal view, the left side of the patient is displayed on the left side of the image. Left frontotemporal hypometabolism is present with a pixel size of 6693 and a Z-score of 5.06.

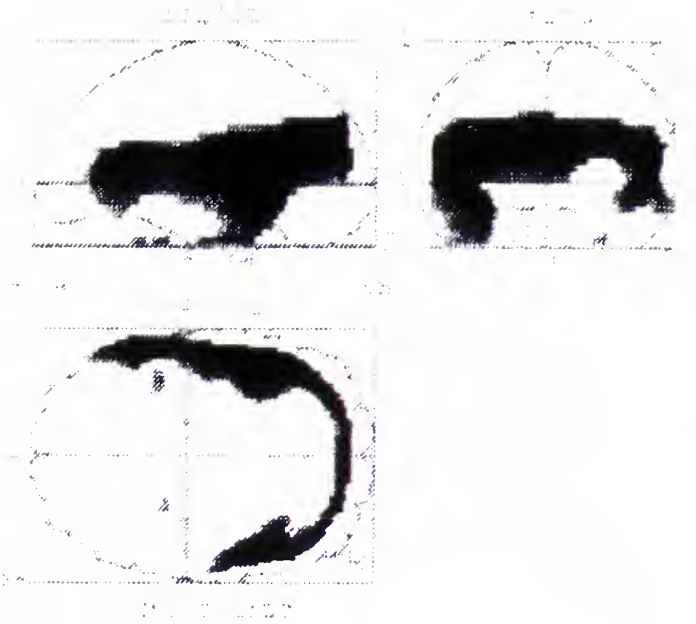

Figure 3. PET image for SPM analysis from Patient 34 with a poor surgical outcome. The surgery was located on the left side, and the pathology report revealed hippocampal sclerosis. Sagittal, coronal, and transaxial views are shown. On the coronal view, the left side of the patient is displayed on the left side of the image. Bilateral (left > right) frontotemporal is present with a pixel size of 3305 and a Z-score of 4.87.

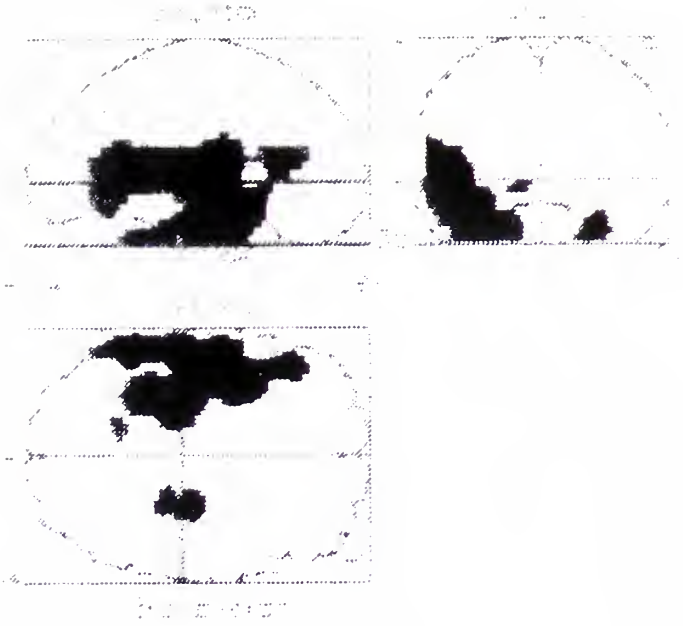

Figure 4. PET image for SPM analysis from Patient 32 with a poor surgical outcome. The surgery was located on the left side, and the pathology report revealed hippocampal sclerosis and non-hippocampal gliosis. Sagittal, coronal, and transaxial views are shown. On the coronal view, the left side of the patient is displayed on the left side of the image. Left frontotemporal hypometabolism is present with a pixel size of 6693 and a Z-score of 5.06. Contralateral right perihippocampal hypometabolism is also present with a pixel size of 140 and a Z-score of 4.36.

Pathology and Temporal Lobe Hypometabolism

Histopathologic correlation was available for 33 patients. Results are summarized in Table 3. Microscopic examination of resected temporal lobe tissue revealed the following: hippocampal sclerosis in 18 patients; hippocampal sclerosis and non-hippocampal gliosis in 7 cases, non-hippocampal gliosis in 5 cases, hippocampal sclerosis and heterotopia in 1 case, hippocampal hemorrhage in 1 case, and heterotopia in 1 case.

Visual PET image analysis revealed that 23/25 (92%) patients with hippocampal sclerosis or hippocampal sclerosis and non-hippocampal gliosis demonstrated ipsilateral temporal lobe hypometabolism that included the medial, anterior, and inferior regions. One scan was normal. One scan contained a defect in the frontal lobe. More detailed regional analysis showed medial ≥ lateral hypometabolism in 20/25, anterior ≥ posterior in 22/25, inferior ≥ superior in 23/25 patients. Ipsilateral frontal extension of the hypometabolic zone was present in 8/25, parietal extension in 4/25, and occipital extension in 3/25. By SPM analysis, 24/25 cases had ipsilateral temporal lobe hypometabolism.

	Regional Temporal Lobe Hypometabolism			Pt.
Pathology	Medial vs. Lateral	Anterior vs. Posterior	Inferior vs. Superior	No.
hipp sclerosis	medial>lateral	anterior>posterior	inferior>superior	18
hipp sclerosis	medial>lateral	anterior>posterior	inferior>superior	31
hipp sclerosis	medial>lateral	anterior>posterior	inferior>superior	2
hipp sclerosis	medial>lateral	anterior=posterior	inferior>superior	11
hipp sclerosis	medial>lateral	anterior=posterior	inferior>superior	9
hipp sclerosis	medial>lateral	anterior	inferior	4
hipp sclerosis	medial=lateral	anterior>posterior	inferior>superior	5
hipp sclerosis	medial=lateral	anterior>posterior	inferior>superior	20
hipp sclerosis	medial=lateral	anterior>posterior	inferior>superior	7
hipp sclerosis	medial=lateral	anterior>posterior	inferior>superior	12
hipp sclerosis	medial=lateral	anterior=posterior	inferior>superior	34
hipp sclerosis	medial=lateral	anterior=posterior	inferior>superior	16
hipp sclerosis	medial=lateral	anterior=posterior	inferior=superior	13
hipp sclerosis	medial=lateral	anterior	inferior>superior	15
hipp sclerosis	medial<lateral	anterior>posterior	inferior>superior	24
hipp sclerosis	medial<lateral	anterior=posterior	inferior>superior	23
hipp sclerosis	medial<lateral	anterior=posterior	inferior>superior	14
hipp sclerosis	normal			1
hipp sclerosis, gliosis	medial>lateral	anterior>posterior	inferior>superior	32
hipp sclerosis, gliosis	medial>lateral	anterior=posterior	inferior>superior	17
hipp sclerosis, gliosis	medial>lateral	anterior	inferior>superior	22
hipp sclerosis, gliosis	medial>lateral	anterior	inferior	6
hipp sclerosis, gliosis	medial=lateral	posterior	inferior	28
hipp sclerosis, gliosis	medial	anterior	inferior	10
hipp sclerosis, gliosis	no temporal defect			33
hipp sclerosis, heterotopia	medial=lateral	anterior>posterior	inferior>superior	21
gliosis	medial>lateral	anterior>posterior	inferior>superior	25
gliosis	medial>lateral	anterior>posterior	inferior	26
gliosis	medial=lateral	anterior=posterior	inferior=superior	30
gliosis	medial=lateral	anterior=posterior	inferior=superior	29
gliosis	normal			35
heterotopia	lateral	anterior=posterior	inferior>superior	36
none	medial>lateral	anterior>posterior	inferior>superior	8
none	medial>lateral	anterior	inferior	27
none	medial=lateral	anterior>posterior	inferior>superior	3
old hemorrhage in hipp	medial>lateral	anterior>posterior	inferior>superior	19

Table 3. Results of pathology and regional location of temporal lobe hypometabolism. Abbreviations: hipp = hippocampus; gliosis = non-hippocampal gliosis.

DISCUSSION

SPM As a Useful Analytic Tool for Epilepsy

PET images of regional cerebral metabolism have proven useful for the localization of seizure foci in patients with complex partial epilepsy. These images are most commonly interpreted through visual analysis. The reader is asked to compare homologous brain regions in order to identify areas of relative hypometabolism. The reader is then asked to map these functional abnormalities to specific anatomic structures/areas within the brain. These areas are then considered as potential sources for that patient's seizure activity. Both tasks can be difficult for the inexperienced observer, leading to interpretive error. A more objective and consistent means of image analysis would be useful for the evaluation of patients with epilepsy.

A number of quantitative/semi-quantitative methods for PET data analysis have been described. These include absolute quantification of regional cerebral glucose metabolism and ratio based region of interest analysis. Absolute quantification requires invasive blood sampling during acquisition of the PET data, as well as complex mathematical manipulation of the acquired data. Ratio based analyses are semi-quantitative and are not useful for the detection of bilateral or diffuse abnormalities.

We have proposed using a new tool, statistical parametric mapping (SPM), for the objective analysis of FDG PET brain images in epilepsy. SPM is a powerful statistical method of localizing differences in regional cerebral metabolism. The patient's image data are compared on a voxel by voxel basis to data from a group of normal, healthy control subjects using the Student's t test. The results are displayed as a statistical map that represents images of change significance. These maps are thresholded such that voxels reaching a specified level of significance are highlighted. The theoretical advantages of

SPM include its objectivity, precise anatomic localization of functional abnormalities, avoidance of blood sampling, and the ready identification of diffuse and bilateral abnormalities.

In this paper, we compared SPM to visual analysis of PET brain scans for the detection of seizure foci and prediction of post-surgical outcome in complex partial epilepsy. We found that SPM analysis identified the seizure focus, as defined by the eventual surgical resection site, in 32/36 (89%) patients that were evaluated. The SPM defined seizure site correlated with the surgical site in 28/31 (90%) patients who had good outcomes. These results are in agreement with the outcome of our own visual PET analysis and with published literature values that describe the utility of PET for seizure site identification (2,20-23). We conclude that SPM analysis is useful for the evaluation of PET data in epilepsy, and may provide an objective and sensitive means of seizure site identification.

To the best of our knowledge, this is the first report of the use of SPM for FDG PET analysis in epilepsy. There has been one prior report, however, on the use of "statistical parametric imaging" (28). In this paper, the authors performed a statistical analysis that compared temporal lobe uptake of radiopharmaceutical to the patient's own mean global cerebral metabolism. Image data from 17 patients were retrospectively reviewed by the authors; seizure foci for 16/17 patients were correctly lateralized using the statistical method. Unlike our study, patient data was not compared to a normal database of FDG images. Each patient served as his/her own control. It is therefore possible that regional hypometabolism was underestimated, and that areas of abnormality were not detected due to some level of global cerebral hypometabolism. Study of larger groups of patients would be necessary to determine whether our SPM method of data analysis is more sensitive than statistical parametric imaging for the detection of localized seizure foci.

Implications of Bilaterality and Extratemporal Extensions

It is interesting to note that SPM analysis identified significant regions of hypometabolism both adjacent to and remote from the primary temporal focus of abnormality. When visual and SPM analyses were compared, it was clear that SPM more consistently identified extratemporal lobe extension of abnormal hypometabolism. This extended area most commonly involved the frontal lobe, but on occasion included the parietal or occipital cortex, and sometimes implicated the contralateral temporal lobe and hippocampus.

Some published reports suggest that extratemporal lobe foci of hypometabolism connote a poor prognosis (22,38), while other reports show no discernable difference (23,39) in patient outcome. Our own results are preliminary, and not conclusive in this regard. We found that 29/36 patients had extratemporal lobe extension of hypometabolism on SPM analysis. This extratemporal extension was subjectively graded as "severe" in 9 cases. When these 9 cases were reviewed, it was determined that 6 of the 31 patients with good post-surgical outcomes had diffuse hypometabolism on SPM analysis, while 3 of the 5 patients with poor post-surgical outcomes had severe extratemporal extension of hypometabolism. Unfortunately, the number of patients with poor surgical outcome in our study, as well as in the other studies referenced above, is too small to draw any definite conclusions regarding a correlation between extratemporal lobe hypometabolism and prognosis in complex partial epilepsy.

The pathophysiologic significance of extratemporal/bilateral hypometabolism on PET images of temporal lobe epilepsy is not clear. This scintigraphic finding may reflect deafferentation, with defective neuronal connections and projections between the hippocampus and temporal, extratemporal, and contralateral sites (40). These connections may be very fine; their detection might be facilitated by the use of SPM rather than the more

gross inspections made through visual analysis. Alternatively, extratemporal lobe hypometabolism may suggest a widespread ultrastructural brain abnormality that could have resulted from a congenital defect during critical periods of brain development (41).

Comparison of Regional Temporal Hypometabolism to Histopathology

Hippocampal sclerosis is a histopathologic diagnosis associated with temporal lobe epilepsy (41). Hippocampal sclerosis can be detected on MRI (42,43), and has been associated with PET temporal lobe hypometabolism (44). In our study, we subdivided the temporal lobe into medial, lateral, anterior, posterior, inferior, and superior regions during visual analysis. We found that 23/25 (92%) scans of patients with hippocampal sclerosis (± non-hippocampal gliosis) had inferior anteromedial temporal hypometabolism. This suggests that PET imaging may provide important non-invasive evidence for the presence of hippocampal sclerosis.

Limitations of the Study

This study was limited by the small size of the epilepsy patient, and especially of the healthy control, study groups. It is possible that comparison of patient data to a larger, more diverse population of healthy control subjects could reveal more limited areas of PET brain hypometabolism, and less extensive extratemporal extension of metabolic abnormality.

This study was also limited by the absence of a literature based definition for the range of SPM significance. It is still unclear whether SPM readings should be based solely on z score, on the number of significant voxels, or on a combination of both criteria. In this study, the area of greatest z score significance was selected as the most likely seizure focus.

CONCLUSIONS

In this study, SPM analysis of FDG PET brain images was as sensitive as visual analysis for the localization of seizure foci and for the prediction of favorable clinical outcome after epilepsy surgery. We would encourage the development of SPM as a supplement or alternative to visual analysis due to the ease of use and reproducibility of interpretation. SPM is also useful for quantitative research analysis which can be compared to clinical data, imaging modalities such as SPECT and MRI, and pathology data such as hippocampal cell loss.

SPM analysis revealed significant extension of PET hypometabolism to extratemporal brain regions. This finding may reflect the connections and projections of neurons from the hippocampus to other temporal lobe, extratemporal lobe, and contralateral sites. Alternatively, this widespread functional abnormality may result from developmental brain damage that includes extratemporal brain regions.

Future directions for SPM would include creation of a large normal database of healthy subjects, and creation of more rigid interpretation criteria regarding the size and level of z score significance required to pinpoint the seizure focus. Continued investigation of the utility of SPM for the localization of both temporal lobe and extratemporal lobe epilepsies should be pursued. As more data is acquired, patterns may emerge that will enhance the likelihood of image based detection of epileptic foci.

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APPENDIX

PET - Epilepsy Data Form

ID Label:

Name:
Date of PET:
ID Number:

Reader 1 = Dr. Holley Dey
2 = Dr. Rajesh Krishnamurthy

Overall Category
1 = normal
2 = temporal lobe only
3 = temporal with frontal extension
4 = temporal with parietal extension
5 = temporal with occipital extension
6 = temporal with other extension
7 = frontal lobe only
8 = frontal lobe with extension
9 = parietal lobe only
10 = parietal lobe with extension
11 = occipital lobe only
12 = occipital lobe with extension
13 = other (describe below)

Bilateral 1 = Yes

Notes

REGION 1

Lobe	1 = temporal		5 = cerebellar		
	2 = frontal		6 = thalamus		
	3 = parietal		7 = basal ganglia		
	4 = occipital				
Area 1	1 = med.	2 = lat.	3 = med. + lat.		
	4 = med. > lat.		5 = lat. > med.		
Area 2	1 = ant.	2 = post.	3 = ant. +post.		
	4 = ant. > post.		5 = post. > ant.		
Area 3	1 = sup.	2 = inf.	3 = sup. + inf.		
	4 = sup. > inf.		5 = inf. > sup.		
Sp. Type	1 = focal	2 = diffuse/patchy			
Side	1 = left	2 = right			
	3 = bilateral left = right				
	4 = bilateral left > right				
	5 = bilateral right > left				
Metabol.	1 = hypomet.	2 = hypermet.			
Asym. Index	1	Absolute Index	1 = < 5% (none)		
	2		2 = 5-10% (minimal)		
	3		3 = 10-15% (mild)		
	4		4 = 15-20% (moderate)		
	5		5 = > 20% (severe)		
	6		6 = post op (missing)		

REGION 2

Lobe	1 = temporal		5 = cerebellar		
	2 = frontal		6 = thalamus		
	3 = parietal		7 = basal ganglia		
	4 = occipital				
Area 1	1 = med.	2 = lat.	3 = med. + lat.		
	4 = med. > lat.		5 = lat. > med.		
Area 2	1 = ant.	2 = post.	3 = ant. +post.		
	4 = ant. > post.		5 = post. > ant.		
Area 3	1 = sup.	2 = inf.	3 = sup. + inf.		
	4 = sup. > inf.		5 = inf. > sup.		
Sp. Type	1 = focal	2 = diffuse/patchy			
Side	1 = left	2 = right			
	3 = bilateral left = right				
	4 = bilateral left > right				
	5 = bilateral right > left				
Metabol.	1 = hypomet.	2 = hypermet.			
Asym. Index	1	Absolute Index	1 = < 5% (none)		
	2		2 = 5-10% (minimal)		
	3		3 = 10-15% (mild)		
	4		4 = 15-20% (moderate)		
	5		5 = > 20% (severe)		
	6		6 = post op (missing)		

REGION 3

Lobe	1 = temporal		5 = cerebellar		
	2 = frontal		6 = thalamus		
	3 = parietal		7 = basal ganglia		
	4 = occipital				
Area 1	1 = med.	2 = lat.	3 = med. + lat.		
	4 = med. > lat.		5 = lat. > med.		
Area 2	1 = ant.	2 = post.	3 = ant. +post.		
	4 = ant. > post.		5 = post. > ant.		
Area 3	1 = sup.	2 = inf.	3 = sup. + inf.		
	4 = sup. > inf.		5 = inf. > sup.		
Sp. Type	1 = focal	2 = diffuse/patchy			
Side	1 = left	2 = right			
	3 = bilateral left = right				
	4 = bilateral left > right				
	5 = bilateral right > left				
Metabol.	1 = hypomet.	2 = hypermet.			
Asym. Index	1	Absolute Index	1 = < 5% (none)		
	2		2 = 5-10% (minimal)		
	3		3 = 10-15% (mild)		
	4		4 = 15-20% (moderate)		
	5		5 = > 20% (severe)		
	6		6 = post op (missing)		

REGION 4

Lobe	1 = temporal		5 = cerebellar		
	2 = frontal		6 = thalamus		
	3 = parietal		7 = basal ganglia		
	4 = occipital				
Area 1	1 = med.	2 = lat.	3 = med. + lat.		
	4 = med. > lat.		5 = lat. > med.		
Area 2	1 = ant.	2 = post.	3 = ant. +post.		
	4 = ant. > post.		5 = post. > ant.		
Area 3	1 = sup.	2 = inf.	3 = sup. + inf.		
	4 = sup. > inf.		5 = inf. > sup.		
Sp. Type	1 = focal	2 = diffuse/patchy			
Side	1 = left	2 = right			
	3 = bilateral left = right				
	4 = bilateral left > right				
	5 = bilateral right > left				
Metabol.	1 = hypomet.	2 = hypermet.			
Asym. Index	1	Absolute Index	1 = < 5% (none)		
	2		2 = 5-10% (minimal)		
	3		3 = 10-15% (mild)		
	4		4 = 15-20% (moderate)		
	5		5 = > 20% (severe)		
	6		6 = post op (missing)		

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